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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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10/071,976

02/05/2002

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10/01/2003

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EXAMINER

NASHED, NASHAAT T

ART UNIT

PAPER NUMBER

1652

DATE MAILED: 10/01/2003

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.
10/071,979

Applicant(s)
Tsien et al.

Examiner
Nashaat T. Nashed

Art Unit
1652



-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE three MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on Feb 5, 2002
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 2-22 is/are pending in the application.
- 4a) Of the above, claim(s) 8-22 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 2-7 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.
If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

- 13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
a) ☐ All b) ☐ Some* c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
*See the attached detailed Office action for a list of the certified copies not received.
- 14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).
a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

- 1) ☐ Notice of References Cited (PTO-892) 4) ☐ Interview Summary (PTO-413) Paper No(s). _____
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948) 5) ☐ Notice of Informal Patent Application (PTO-152)
- 3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s). 1 6) ☐ Other:

The application has been amended as requested in the communication filed February 5, 2002. Accordingly, claim 1 has been canceled, and claims 2-22 have been entered.

Claims 2-22 are pending.

Restriction to one of the following inventions is required under 35 U.S.C. 121:

- | | |
|-----------|---|
| Group I | Claims 2-7, drawn to a functional engineered mutant <i>Aequorea</i> green fluorescent protein of SEQ ID NO: 2, classified in Class 530, subclasses 350. |
| Group II | Claims 8-13, drawn to a method of identifying a test compound, classified in Class 436, subclass 86. |
| Group III | Claims 14-22, drawn to a method of determining a target, classified in Class 436, subclass 86. |

The inventions are distinct, each from the other because of the following reasons:

Inventions of Groups I and those of Groups II and III are related as product and processes of use. The inventions can be shown to be distinct if either or both of the following can be shown: (1) the process for using the product as claimed can be practiced with another materially different product or (2) the product as claimed can be used in a materially different process of using that product (MPEP § 806.05(h)). In the instant case, the functional engineered mutant *Aequorea* green fluorescent protein can be used in other methods such as in hybridization methods or labeling cellular components.

Inventions of Groups II and III are unrelated. Inventions are unrelated if it can be shown that they are not disclosed as capable of use together and they have different modes of operation, different functions, or different effects (MPEP § 806.04, MPEP § 808.01). In the instant case, the different inventions are independent methods having different steps.

Because these inventions are distinct for the reasons given above and have acquired a separate status in the art as shown by their different classification, restriction for examination purposes as indicated is proper.

During a telephone conversation with Emanuel Vacchiano on July 11, 2003 a provisional election was made with traverse to prosecute the invention of Group I, claims 2-7. Affirmation of this election must be made by applicant in replying to this Office action. Claims 8-22 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention.

Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 C.F.R. § 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a diligently-filed petition under 37 C.F.R. § 1.48(b) and by the fee required under 37 C.F.R. § 1.17(h).

Claims 2-7 are pending and under consideration in this Office action.

The disclosure is objected to because of the following informalities: the figure "□" is found through out the specification instead of Greek letters, Å, and °C, see for example, page 3, line 7; page 15, line 25; page 29, lines 10, 11, 30 and 40; page 37, line 31; page and 43, line 20. Also, Fig 5-1 to Fig 5-28 should be Figure 5A to 5AL.

Appropriate correction is required.

The specification has not been checked to the extent necessary to determine the presence of all possible minor errors. Applicant's cooperation is requested in correcting any errors of which applicant may become aware in the specification.

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 2-7 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claim 48 of U.S. Patent No. 5,777,079 (079). Although the conflicting claims are not identical, they are not patentably distinct from each other because the embodiments of issued claim 48 in the 079 patent encompasses the embodiment of claims 2-7. Claims 48 of the 079 patent is drawn to any double mutant of SEQ ID NO: 2 at position 65 and 203 of SEQ ID NO: 2. The instant claims are limited to

an aromatic amino acid substitution at positions 203 and the mutation of the serine residue at position 65 to G, T, A, L, C, V or I.

The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 102 that form the basis for the rejections under this section made in this Office action:

The following is a quotation of 35 U.S.C. § 103 which forms the basis for all obviousness rejections set forth in this Office action:

A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Subject matter developed by another person, which qualifies as prior art only under subsection (f) or (g) of section 102 of this title, shall not preclude patentability under this section where the subject matter and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. § 103, the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 C.F.R. § 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of potential 35 U.S.C. § 102(f) or (g) prior art under 35 U.S.C. § 103.

Claims 2-7 are rejected under 35 U.S.C. § 103 as being unpatentable over U. S. Patent 5,777,079 (079) in view U. S. Patent 5,804,387 (387, IDS reference P5) and the state of the art.

The 079 patent teaches variant of the *Aequorea* green fluorescent protein (GFP) having the amino acid sequence of SEQ ID NO: 2, see abstract. It teaches and claims variant GFP with substitution mutations at positions 202 or 203, and position 65, see column 4, lines 16 and 17; column 5, lines 14-16; Table I, and claim 48 of the patent. Said substitution mutations causes enhanced fluorescence and change in the color of the light, see Table I. It specifically teaches the substitution of Ser-65 with Ala, Leu, Cys, Val, Ile

or Thr, see column 5, lines 14-16, and the substitution of Tyr-66 with another aromatic amino residues as well as substitution of residues Y145, H148, M153, Val163, and N146, see Table II, column 12. In addition, the 079 patent teaches a fusion protein comprising the above mentioned variants of GFP, see column 6, lines 3-16. The 097 patent, however, does not specifically teaches the substitution mutation of Thr-203 to an aromatic amino acid residue.

The 387 patent teaches that the substitution mutation of F64L, V68L, and S72A of GFP are brighter than the wild-type GFP, see the abstract.

The 079 patent provide one of ordinary skill in the art with a motivation to make new variants of GFP as they teach the usefulness of using different variants having different colors simultaneously, see column 2, line 12-16. The 079 patent teach that mutation of Thr-203 to a more hydrophobic residue produces desirable changes in the fluorescence properties of GFP. The fact that the fluorescence is sensitive to a conservative mutation, i. e., T203I, clearly indicate that Thr-203 is close in space to and interacts with the chromophore of GFP. Thus, it would have been obvious to one of ordinary skill in the art at the time of invention to substitute Thr-203 with an aromatic amino acid residues in any one of the mutants taught in the 079 such as substitutions of Ser-65 and Tyr-66 mutants described in Examples 2 and 3 of the 079 patent (claims 2-5). Aromatic amino acid provide chromphoric amino acids side chains that would enable them to interact physically and optically with the fluorescent chromophore of GFP, and thus, would be expected to attenuate the fluorescence of the GFP chromophore to a larger extent. The ordinary skill in the art would have been further motivated by the teaching of the 387 to incorporate additional substitution mutation in GFP at positions 64, 68, and 72 to further enhance the intensity of the fluorescence of the mutants of GFP (claim 6). It would have been further obvious to one of ordinary skill in the art to make a fusion protein with a peptide of interest such a polyhistadine tag or maltose binding protein for easy purification (claim 7). Thus, the claimed invention was within the ordinary skill in the art to make and use at the time was made and was as a whole, clearly *prima facie* obvious.

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Nashaat T. Nashed, Ph. D. whose telephone number is (703) 305-6586. The examiner can normally be reached Monday, Tuesday, Thursday, and Friday from 9:00 a.m. to 5:30 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapura Achutamurthy, can be reached on (703) 308-3804. The fax phone numbers for this Group are (703) 305-3014 and (703)308-4242.

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Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.


Nashaat T. Nashed, Ph. D.
Primary Examiner